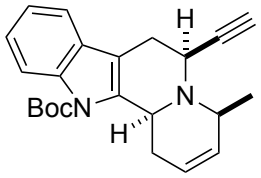
Problem Session (4)

2024/12/27 Hiromu Kakizawa

topic: azides in organic synthesis

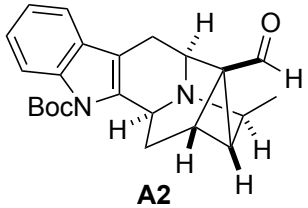
Please explain the mechanisms for the reactions in schemes **A**–**C**.

A



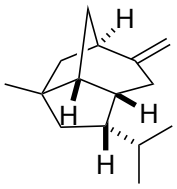
A1

1. TsN_3 (1.8 eq), CuTC (10 mol%)
   toluene, 23 °C, 67%
2. $Rh_2(OAc)_4$ (10 mol%), 1,2-dichloroethane, 80 °C;
   H_2O (23 eq), K_2CO_3 (2.0 eq), MeOH, 23 °C, 48%



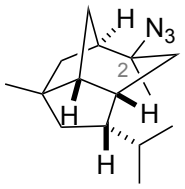
A2

B



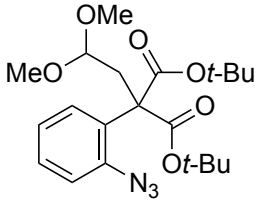
B1

$Co(BF_4)_2 \cdot 6H_2O$ (20 mol%), **B3** (20 mol%)
p-ABSA (3.0 eq), *t*-BuOOH (60 mol%), $PhSiH_3$ (2.0 eq)
EtOH, rt, 77%, dr = 8.4:1 at C2



B2

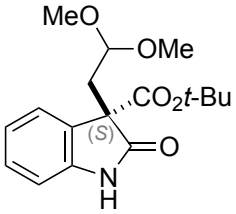
C



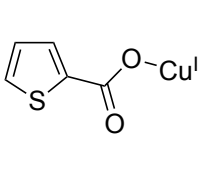
C1

C3 (10 mol%), $[Ir(cod)Cl]_2$ (5.0 mol%)
n-Bu_4NBF_4 (10 mol%), $PhSiH_3$ (3.0 eq), MS4A
cyclohexane, 45 °C, 88% (91% ee)

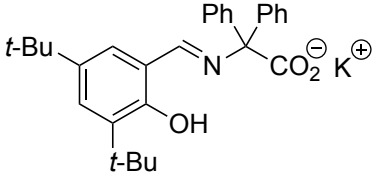
note:
C3 was derived from *trans*-4-hydroxy-L-proline and enantiomerically pure.



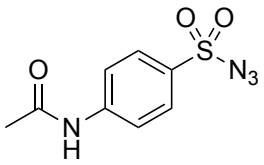
C2
(major enantiomer shown)



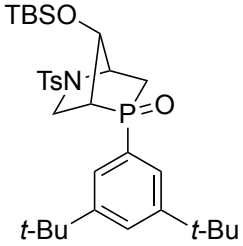
CuTC



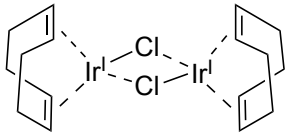
B3



p-ABSA



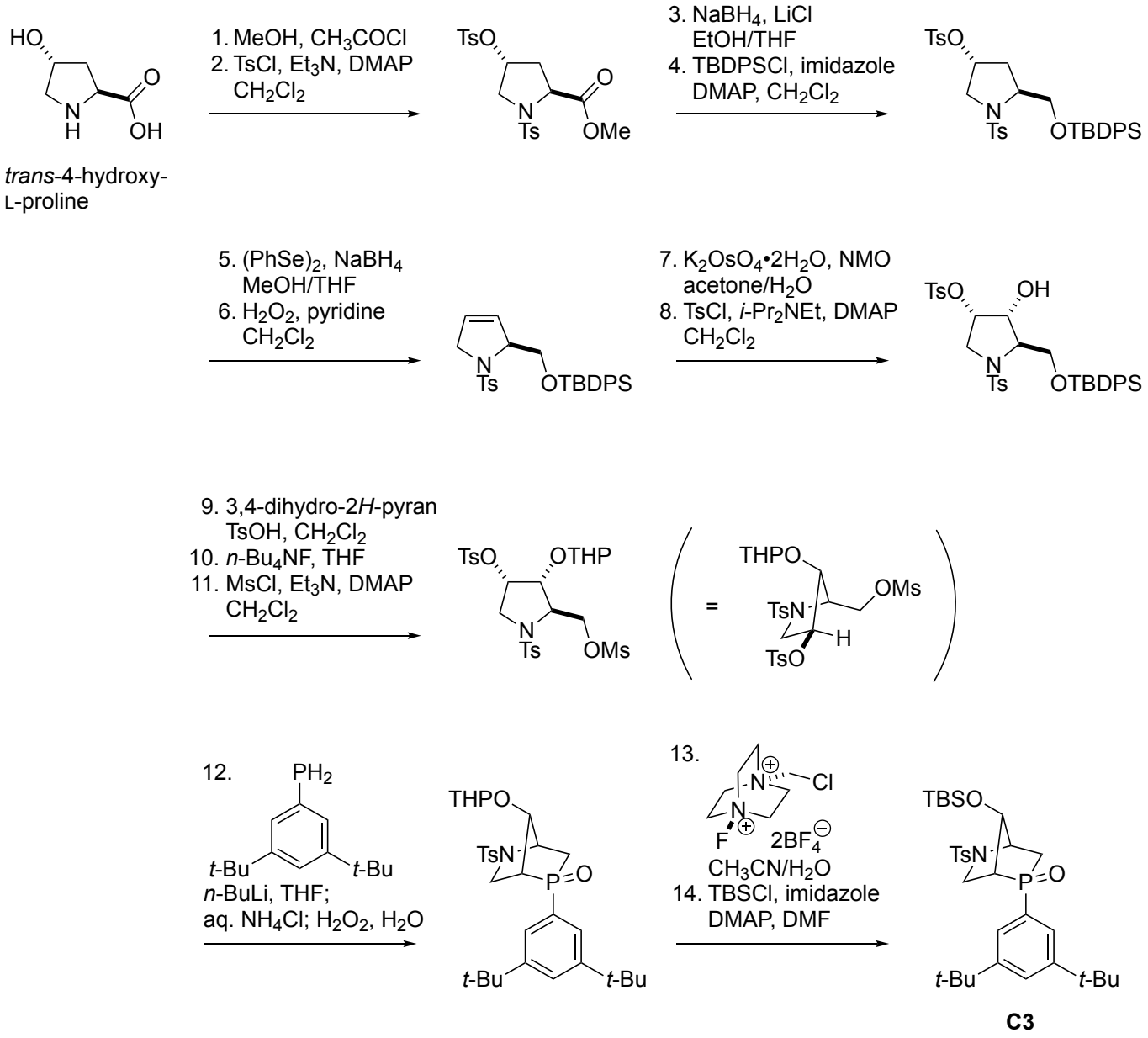
C3



$[Ir(cod)Cl]_2$

Q1

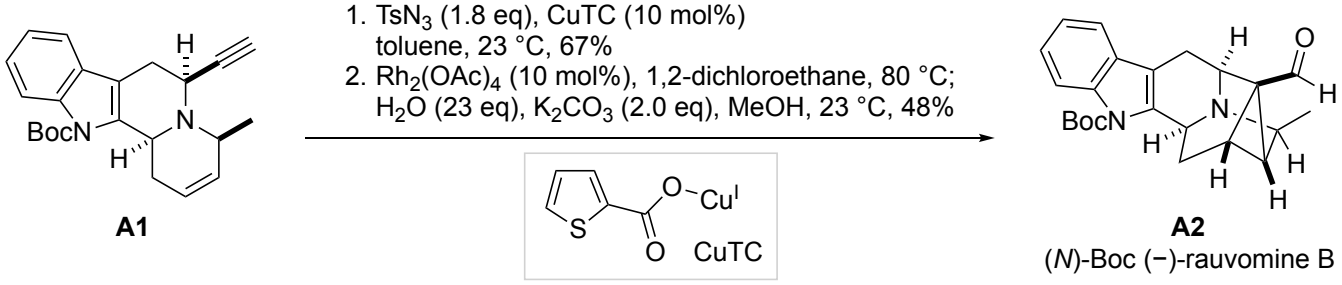
appendix: synthetic scheme of enantiomerically pure phosphine oxide **C3**
(You do not have to give the mechanisms for the reactions below.)



Problem Session (4) -Answer-

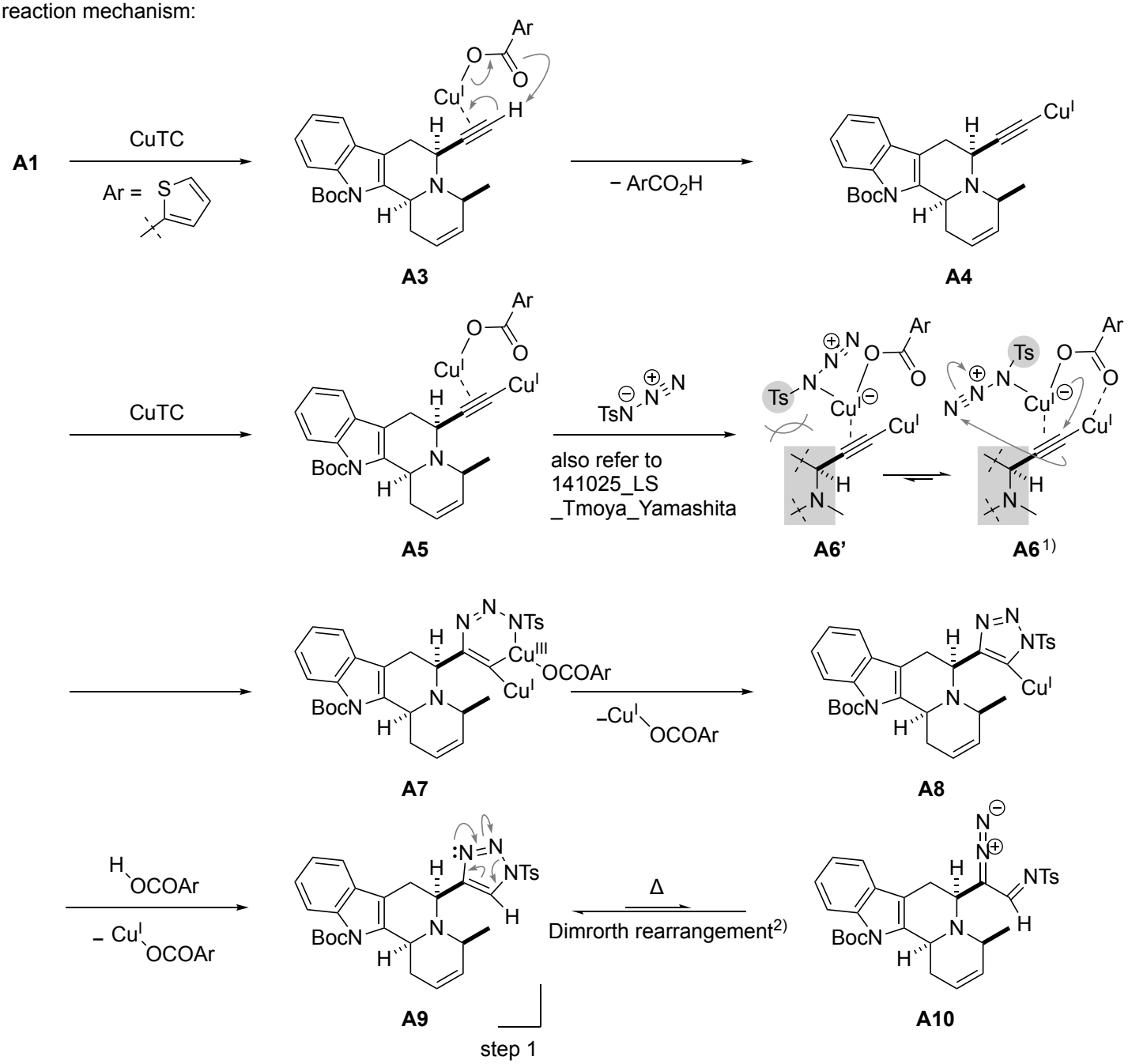
2024/12/27 Hiromu Kakizawa

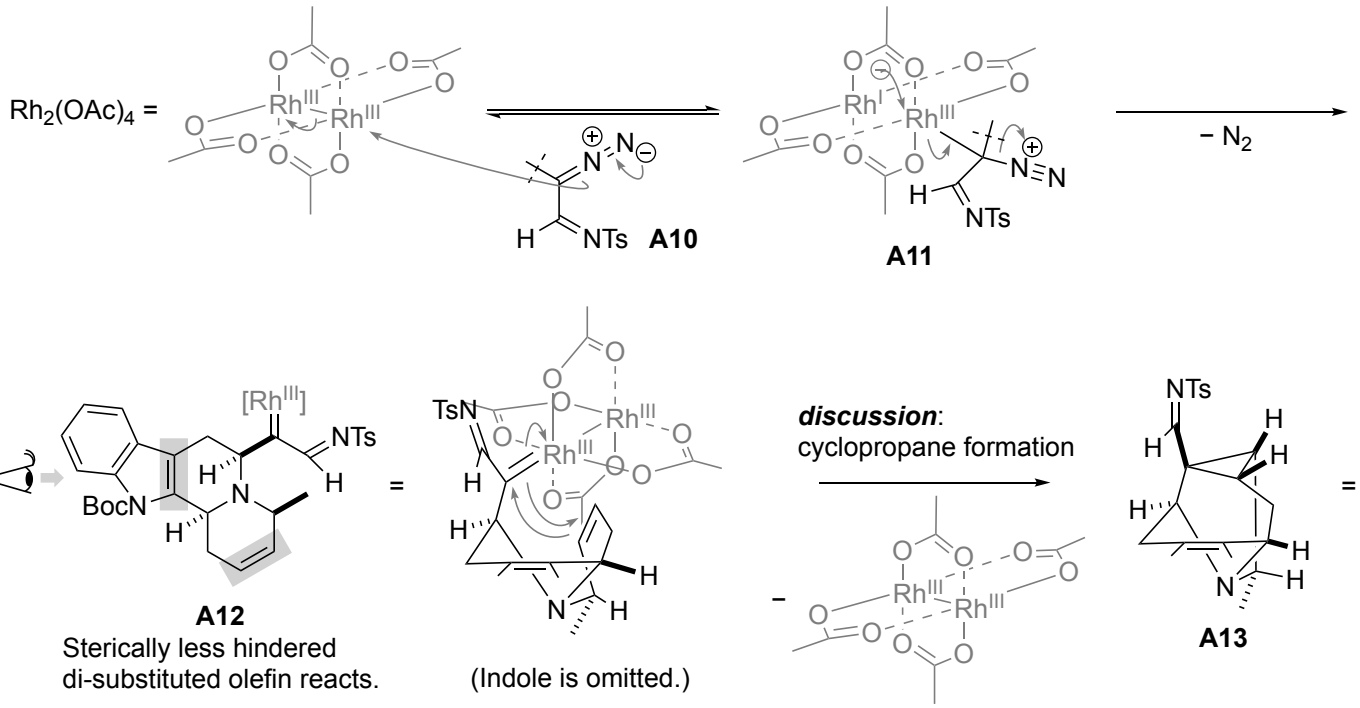
scheme **A** use of azide-alkyne [3+2] cycloadduct; cyclopropanation via formation of rhodium carbenoid



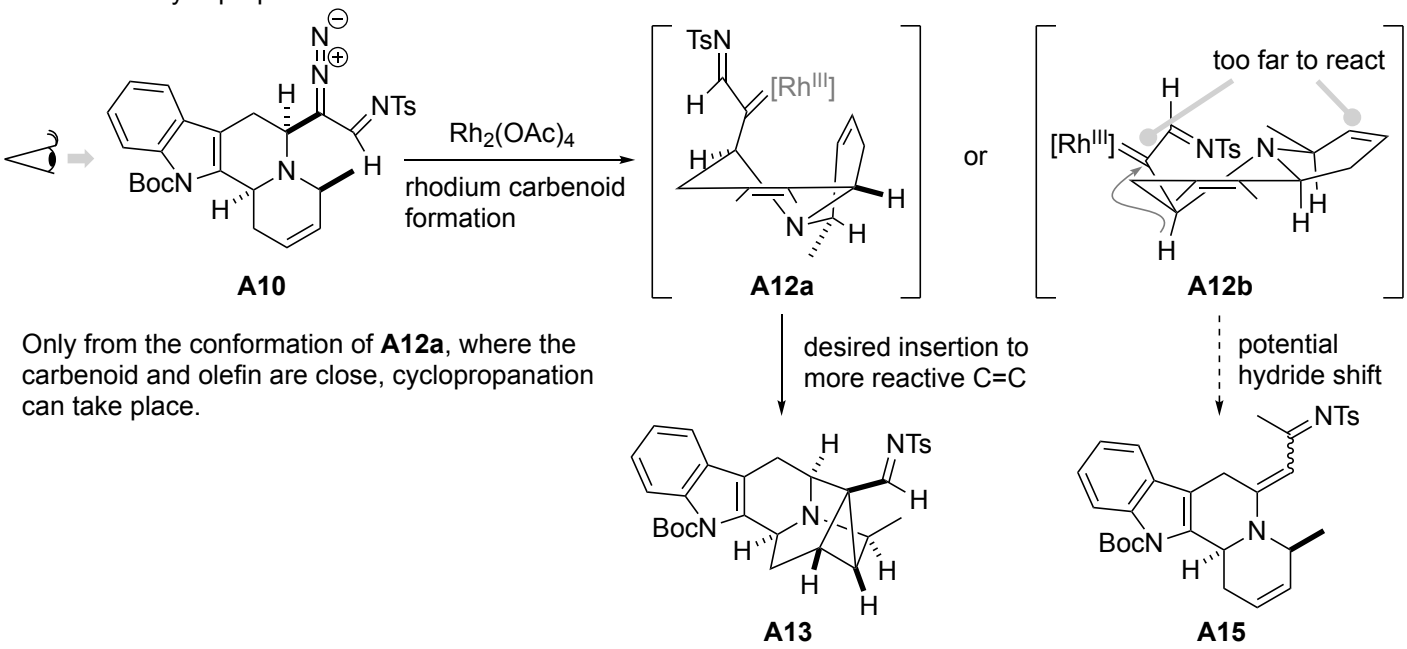
Aquilina, J. M.; Banerjee, A.; Morais, G. N.; Chen, S.; Smith, M. W. *J. Am. Chem. Soc.* **2024**, *146*, 22047.

reaction mechanism:

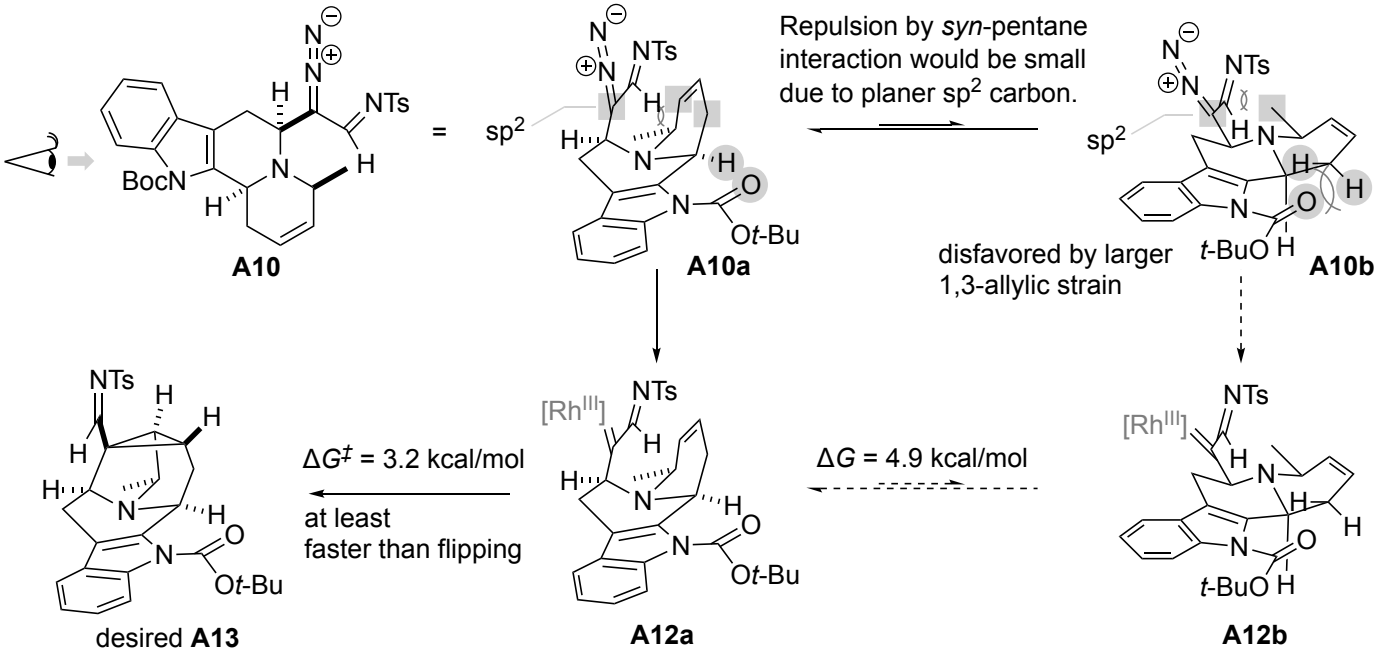




discussion: cyclopropane formation

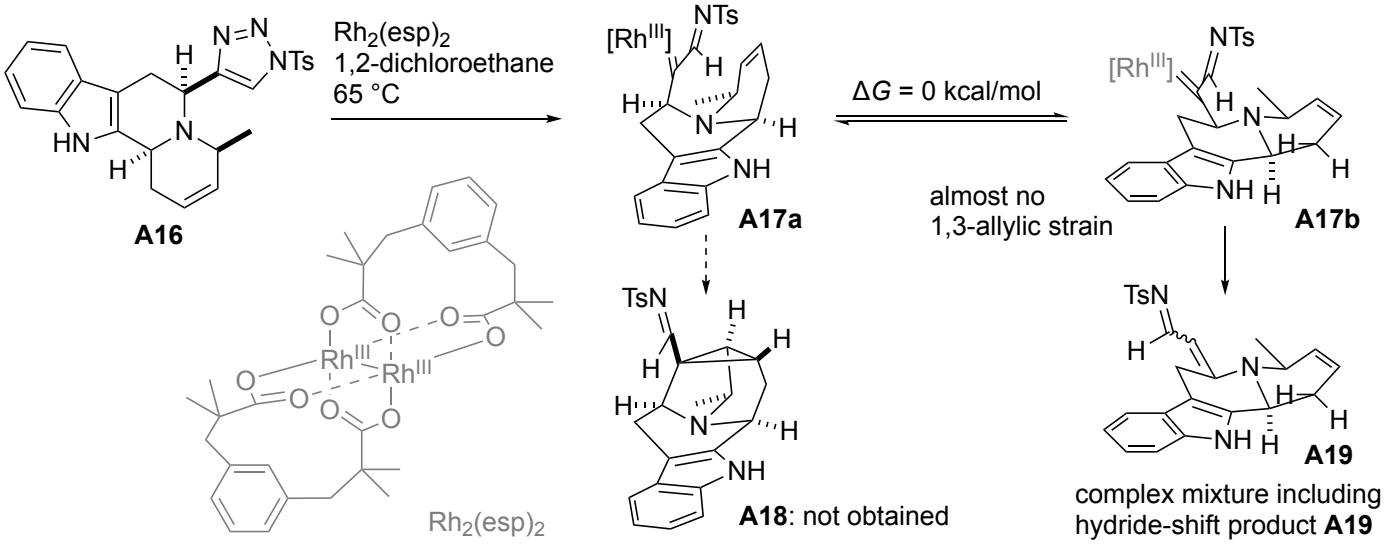


What is the determining factor of conformation of the rhodium carbenoid?



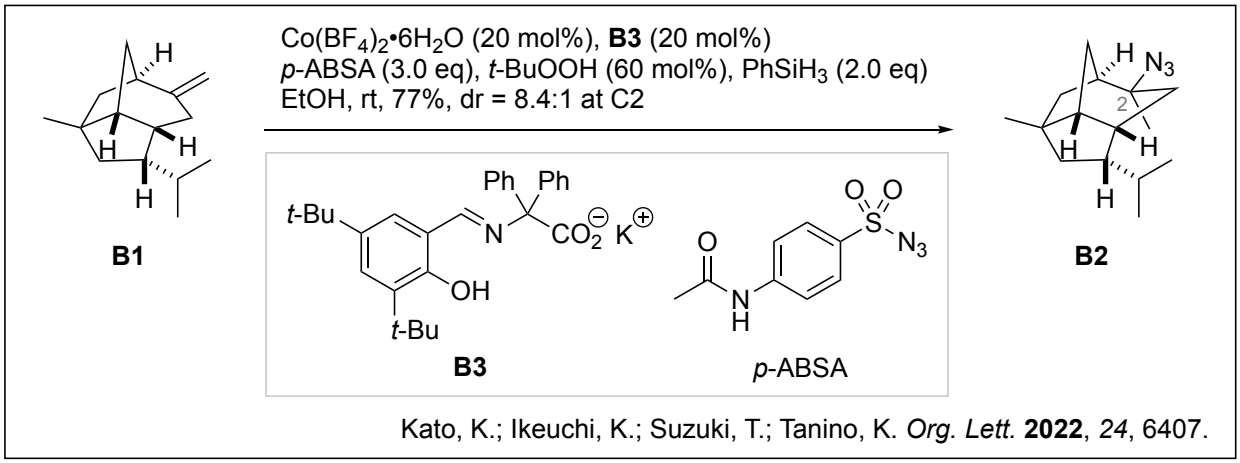
Calculations were conducted by authors at
M06-D3/def2-TZVPP-SDD(Rh), SMD(DCE)//B3LYP-D3/def2-SVP-SDD(Rh) (free energy)
M06-D3/def2-TZVPP-SDD(Rh), SMD(DCE)//B3LYP/def2-SVP-SDD(Rh) (transition state)

In fact, substrate **A16** with unprotected indole partially underwent hydride shift to give **A20**.



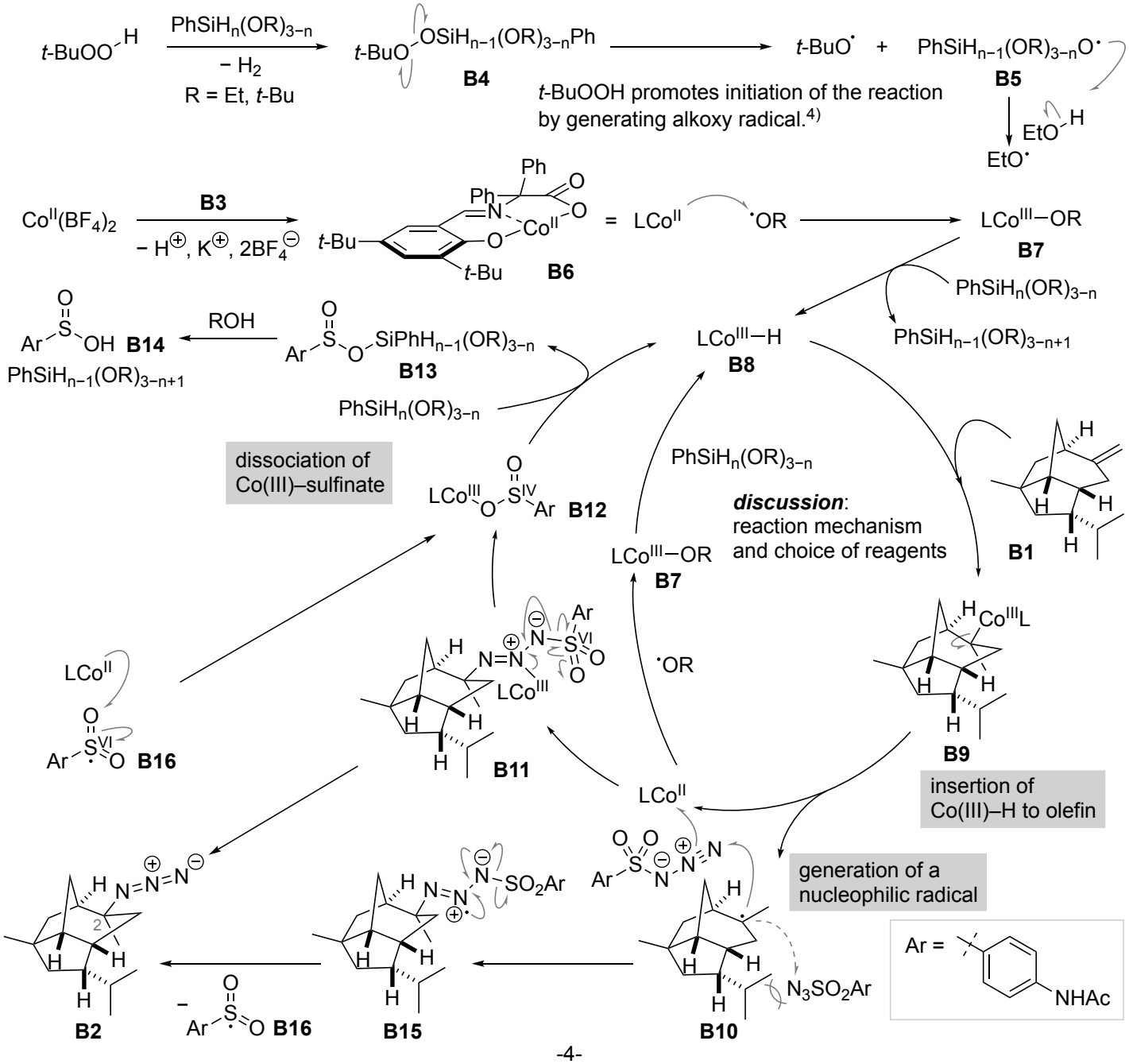
references for scheme **A**
1) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science*, **2013**, *340*, 457.
2) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.*, **2008**, *130*, 14972.

scheme **B** cobalt-catalyzed hydroazidation; synthesis of tertiary azide from olefin



Kato, K.; Ikeuchi, K.; Suzuki, T.; Tanino, K. *Org. Lett.* **2022**, *24*, 6407.

reaction mechanism[3]:

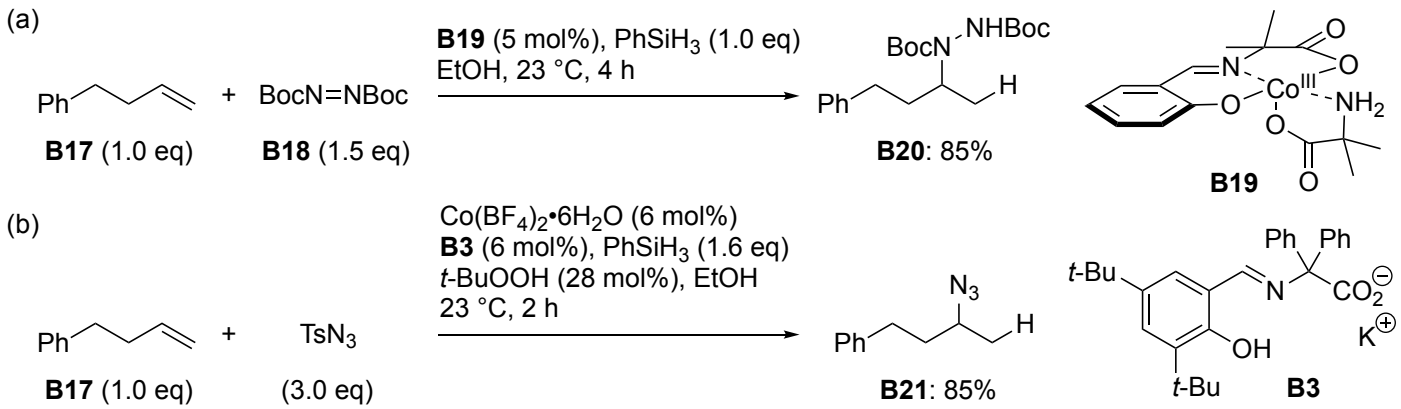


discussion: reaction mechanism and choice of reagents

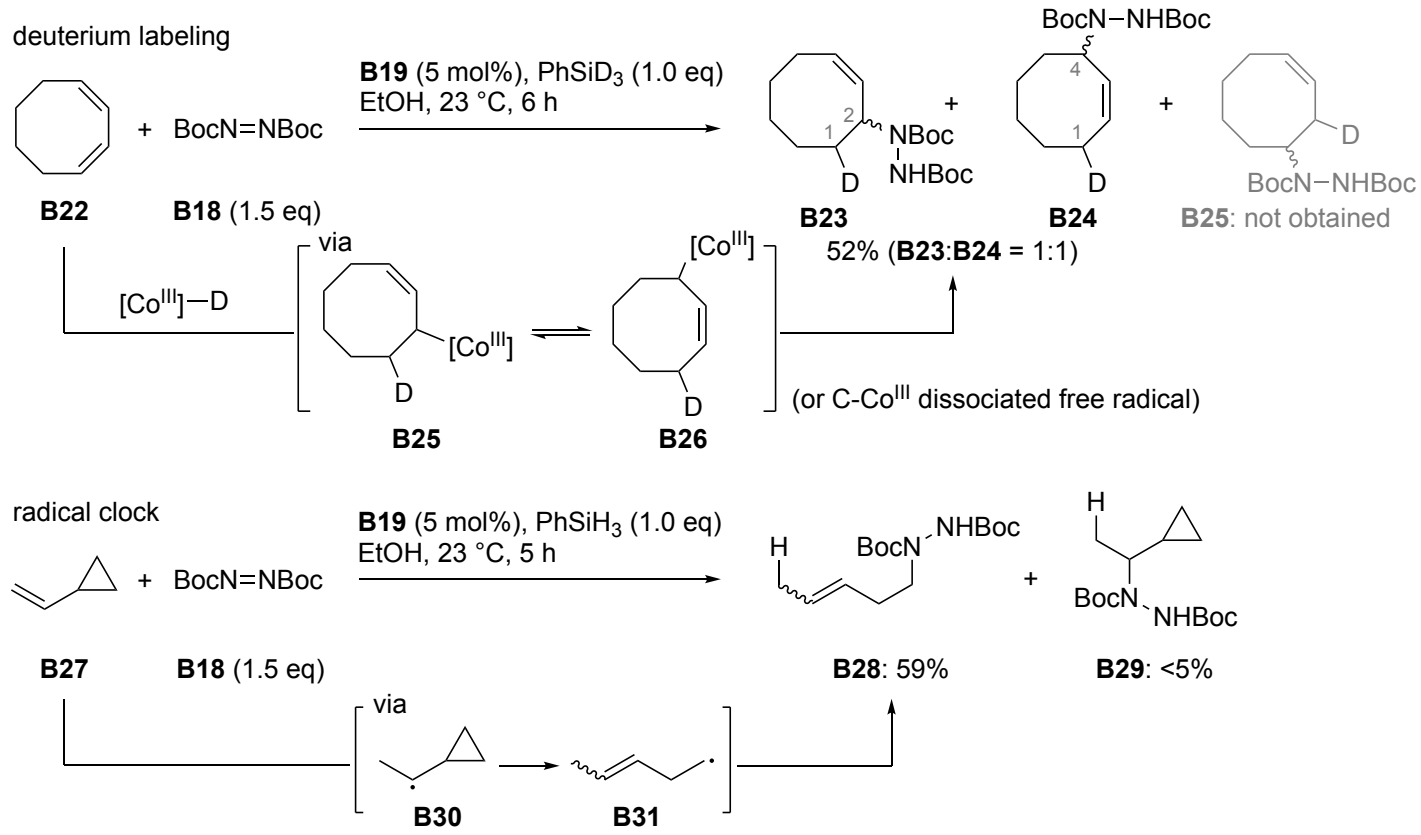
The applied reaction condition for hydroazidation was optimized by Carreira's group. Here shows their mechanistic study and optimization of reagents.[3)]

i) mechanistic study

In their report, they tried to elucidate the mechanisms of the Co-catalyzed reactions below with similar conditions, mainly focusing on hydrohydrazination reaction (scheme (a)).

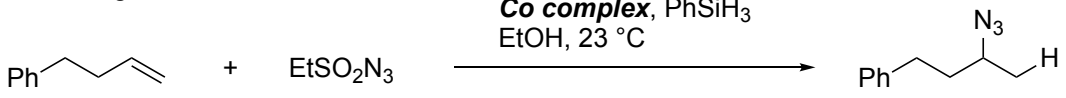


From deuterium labling and radical clock experiments below, they suggested the hydrocobaltation (**B1** -> **B9**) and free radical generation (**B10**).



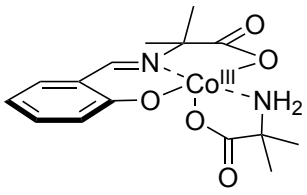
Other reaction intermediates were not isolated or observed by ^{1}H NMR monitoring, but it seems reasonable that the generated radical attacks to azide reagent to give desired azide **B2**.

ii) choice of ligand



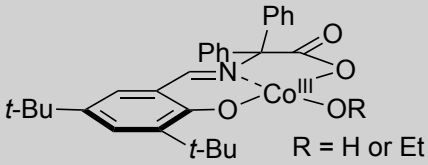
B17 (1.0 eq) **B21**

results with different ***Co complex***:



B19

24 h
B21: 60% yield

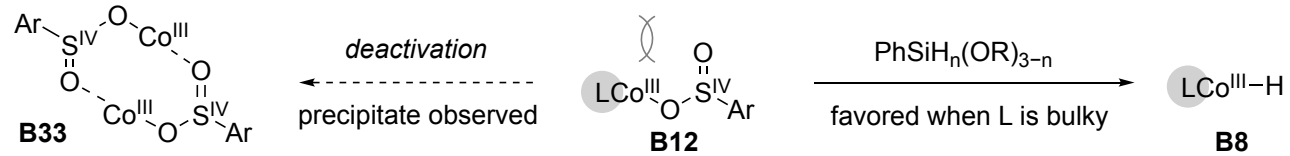


B32 (obtained by mixing $Co(NO_3)_2 \cdot 6H_2O$ and **B3** in ethanol)

8 h
B21: 58% yield

Ligand **B3** with increased bulkiness around Co^{III} center led to much faster reaction.

possible rationale (my proposal):



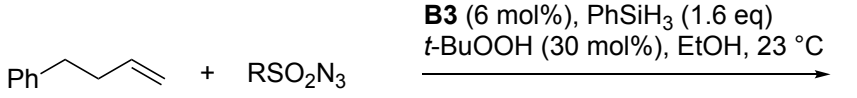
B33 oligomeric Co–sulfinate (proposed by author)

B12

B8

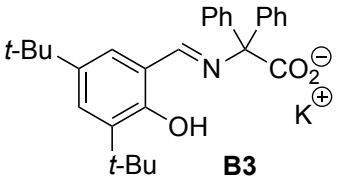
Sulfinate, which is generated from sulfonazide, needs to dissociate from cobalt for catalytic cycle turnover. This dissociation could be helped by bulkiness of the ligand, with large steric repulsion between sulfinate.

iii) choice of azide reagent



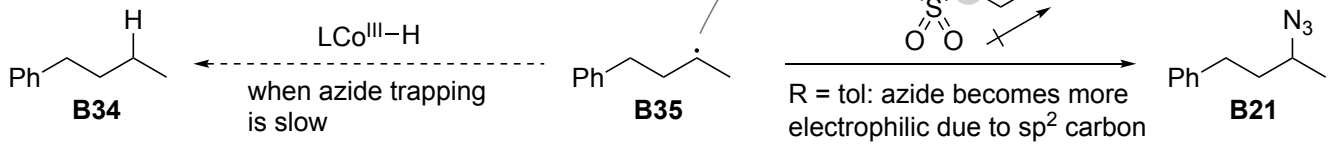
B17 (1.0 eq) (3.0 eq) **B21** **B34**

	R	ratio **B21**:**B34**
1	Et	77:23
2	Me	77:23
3	tol	89:11



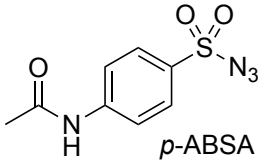
B3

possible rationale (my proposal):



B34 **B35** **B21**

Aryl-substituted sulfonyl azide reacts faster with carbon radical due to increased electrophilicity of azide. TsN_3 needs to be prepared from TsCl and NaN_3, and *p*-ABSA (utilized in the reaction of scheme **B**) would be a commercially available alternative.

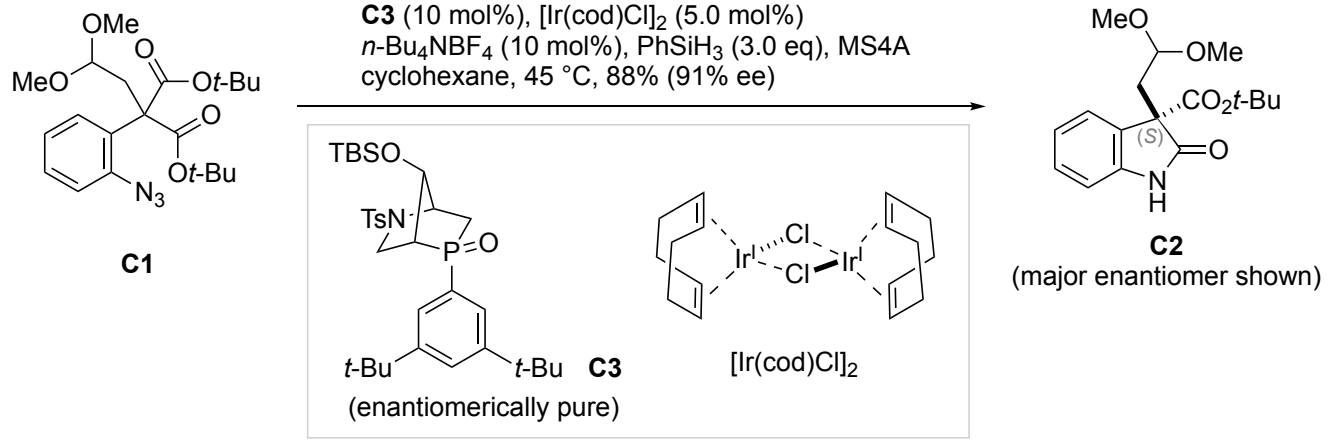


p-ABSA

references for scheme **B**

3) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.*, **2006**, *128*, 11693.
4) Tokuyasu, T.; Kunikawa, S.; Matsuyama, A.; Nojima, M. *Org. Lett.*, **2002**, *4*, 3596.

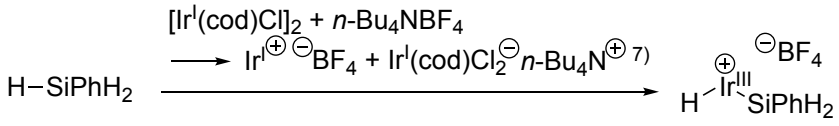
scheme **C** desymmetrization via chiral-phosphine mediated Staudinger-aza-Wittig reaction

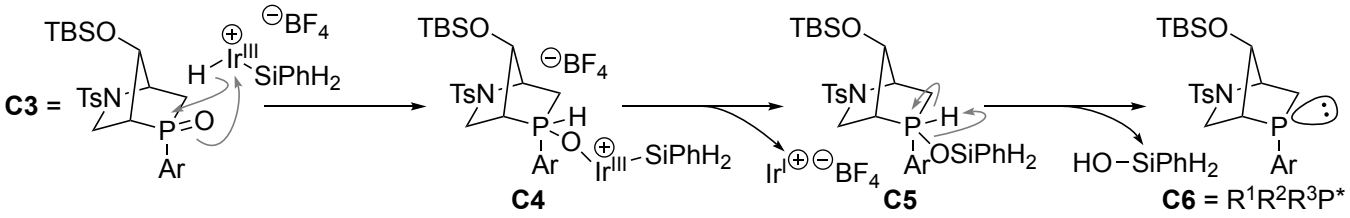


Xie, C.; Kim, J.; Mai, B. K.; Cao, S.; Ye, R.; Wang, X.-Y.; Liu, P.; Kwon, O. *J. Am. Chem. Soc.* **2022**, *144*, 21318.

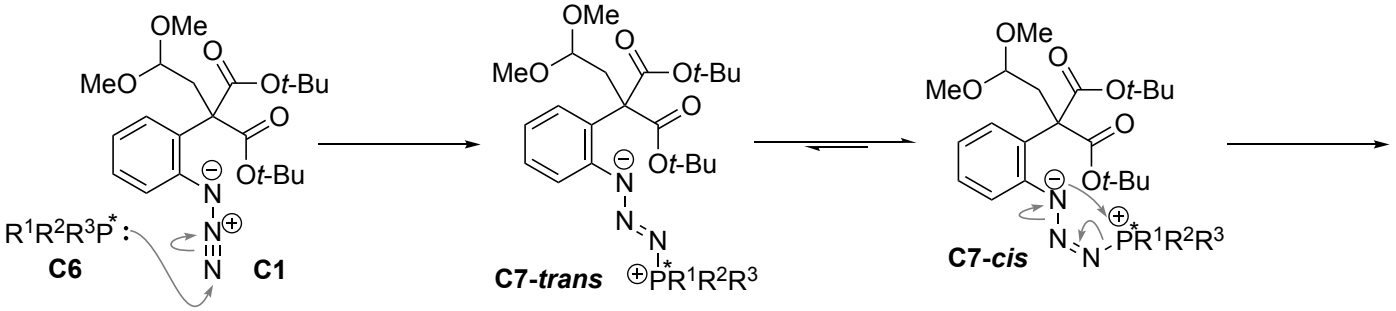
reaction mechanism:

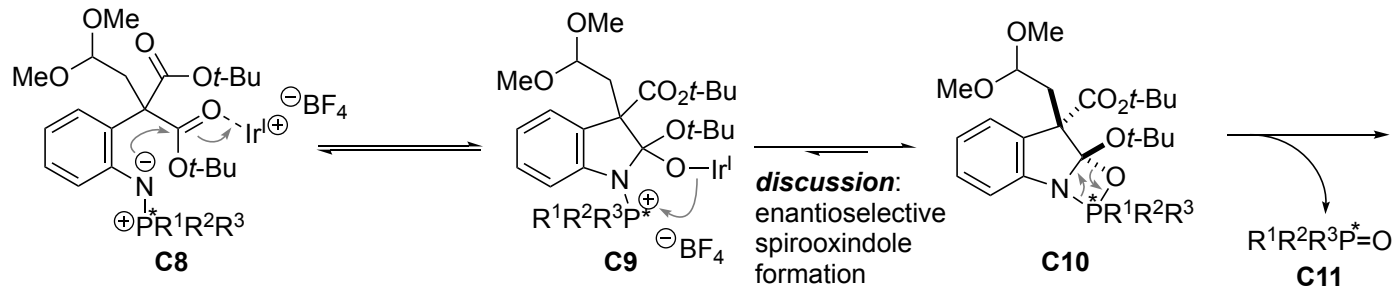
i) generation of active P(III) species (stereoretentive reduction of phosphine oxide by silane[5)6)])

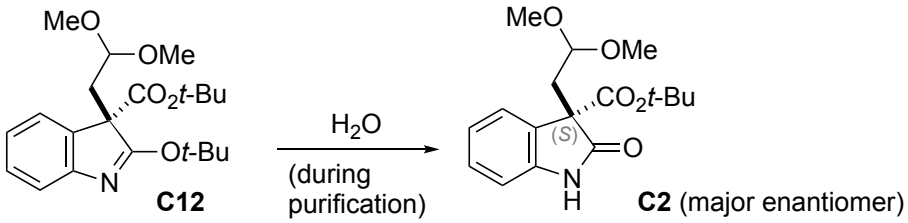




ii) Staudinger aza-Wittig reaction



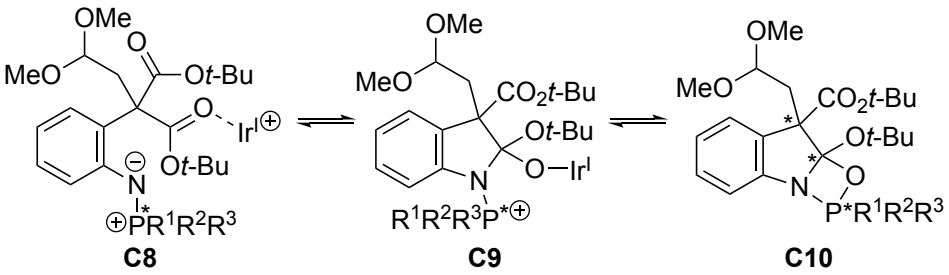




discussion: enantioselective spirooxindole formation (my proposal)

The authors suggest the kinetic explanation for enantioselectivity, calculating the activation barrier for all the possible oxazaphosphethane **C10**.

However, considering the predicted stability of azaylide **C8**, formation of **C10** from **C8** could be reversible and I compared the thermodynamic stability of the oxazaphosphethane intermediates **C10**.



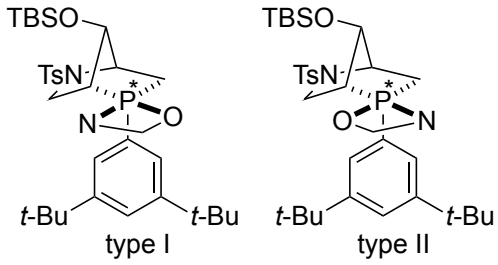
C8 **C9** **C10**

pK_a values (in DMSO)	R, H	$Ph_3P^{\oplus}$, R, H
R = CO_2Et	29.5	8.5
(R = H	56	22.4)
	HN, Ph, H	$Ph_3P^{\oplus}$, N, Ph, H
	30.6	~10?

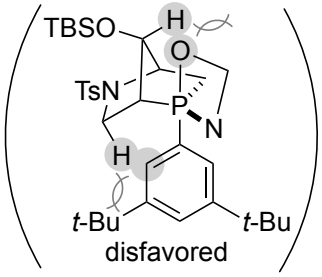
Considering the similar pKa values of aniline and ethyl acetate, at least azaylide **C8** seems stabilized enough.

Four configurations shown below are considered based on the following i) and ii):

i) configuration around P atom: type I and type II considered



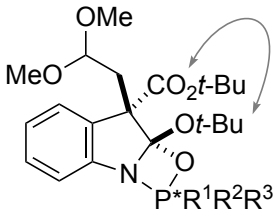
type I type II



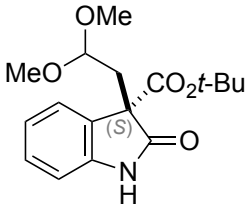
disfavored

ii)

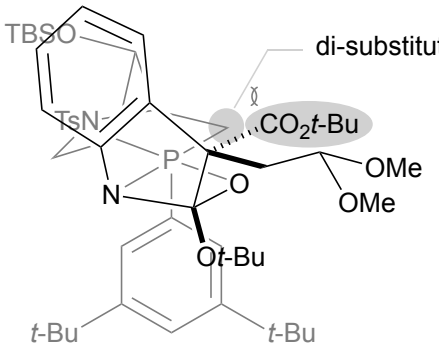
Bulky O*t*-Bu and CO_2t-Bu should be *trans* on indoline.



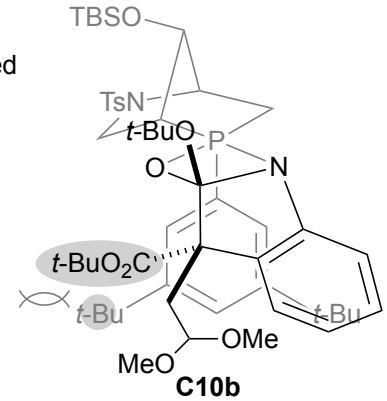
The steric interaction between bulky CO_2t-Bu and P-substituents (derived from **C6**) would determine the stability of oxazaphosphethane.



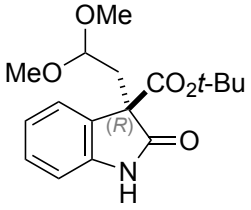
C2 (major enantiomer)



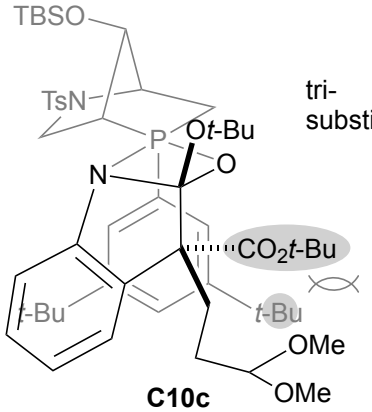
C10a
most favored



C10b
disfavored

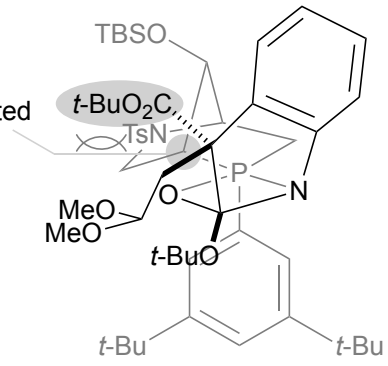


C2' (minor enantiomer)



C10c
disfavored

tri-substituted



C10d
unfavored

references for scheme **C**

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